In The

Supreme Court of the United States

October Term, 1972

No. 72-251

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court Of Appeals for the Fourth Circuit

BRIEF FOR RESPONDENT HYNSON, WESTCOTT AND DUNNING, INCORPORATED

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OPINIONS BELOW

The opinion of the court of appeals (J.A. 173-180)[1] is reported at 461 F.2d 215. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (J.A. 72-78; 36 Fed. Reg. 11763).

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[1] "J.A." refers to the Joint Appendix filed by the parties in this case and in Nos. 72-414, 72-528, 72-555, and 72-666, with which this case has been consolidated.

JURISDICTION

The judgment of the court of appeals (J.A. 181) was entered on May 24, 1972. The petition for a writ of certiorari was filed, pursuant to an extension of time granted by Mr. Justice Rehnquist, on September 7, 1972. On January 8, 1973, this Court granted the petition and consolidated the case with four other cases in which it also granted petitions for a writ of certiorari. The jurisdiction of this Court rests on 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 505(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c); J.A. 477-478) provides in pertinent part:

Within one hundred and eighty days after the filing of [a new drug] application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be

issued within ninety days after the date fixed by the Secretary for filing final briefs.

Section 505(e) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(e); J.A. 479) provides in part:

> "The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *."

21 Code of Federal Regulations, Part 130

(Revised as of January 1, 1969)

[In effect when Hynson, Westcott & Dunning, Incorporated, accepted an opportunity for a hearing before FDA on April 18, 1969]

Section 130.14 Contents of notice of hearing.

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue his order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the FEDERAL REGISTER and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to accept the opportunity for a hearing by written request within 30 days after such notice, a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree.

(c) The hearing will be open to the public: *Provided, however*, That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

[28 F.R. 6377, June 20, 1963, as amended at 29 F.R. 7020, May 28, 1964]

QUESTIONS PRESENTED

1. Whether, despite the evidence submitted by Hynson, Westcott and Dunning, Incorporated, the Commissioner of Food and Drugs may, without a hearing, make a determination that there is a lack of substantial evidence of effectiveness of the drug Lutrexin, within the meaning of the Federal Food, Drug and Cosmetic Act (as amended by the Drug Amendments of 1962) and the Commissioner's regulations and, upon the basis of such determination, withdraw approval of the new drug application for such drug.

2. Whether the regulations under which a hearing was denied are valid.

3. Whether Hynson, Westcott & Dunning was entitled to a hearing by virtue of its timely acceptance of the

proffered opportunity for a hearing under regulations then in effect, regardless of its rights under the regulations thereafter adopted under which a hearing was denied.

SUMMARY OF ARGUMENT

1. In Point I we analyze the affidavits and medical studies submitted by respondent Hynson, Westcott and Dunning, Incorporated (HW&D) to FDA, showing that they raise an issue of material fact as to the effectiveness of Lutrexin. The affidavits and studies and the Commissioner's analysis of them in his order (J.A. 72) show the existence of disputed issues of fact as to whether the medical data contains adequate and well-controlled studies.

2. FDA's so-called "summary judgment" regulations bear little resemblance to the summary judgment requirements of Rule 56 to which the agency has likened them. They are unfair on their face since, unlike the Rule 56 procedures, they permit an *ex parte* decision by the movant (FDA) without the submission of any evidence to support its position, and give the manufacturer no opportunity to show that the medical studies submitted raise a substantial issue of material fact requiring a hearing. Nor do the regulations provide for an impartial decision-maker to pass on the summary judgment question.

The Court of Appeals in the instant case and the Court of Appeals for the District of Columbia Circuit have pointed out these deficiencies in the regulations.

The Commissioner acts as both prosecutor and judge of the validity of his actions. It cannot accurately be said, as the Government does, that the summary judgment procedures of the Federal Trade Commission and the National Labor Relations Board are "similar" to

those of FDA, since those agencies provide for an impartial decision-maker to decide motions for summary judgment.

It is clear from the decisions of this Court that the party moving for summary judgment has the burden of showing the absence of a genuine issue of material fact —a burden which FDA has shifted to the holder of an NDA under its regulations.

The issue in the instant case is one of fact—whether there is substantial evidence of the efficacy of Lutrexin. Under the decisions of this Court, due process requires an opportunity to confront and cross-examine witnesses —a trial-type hearing.

3. The analysis in Point I, *infra*, of the affidavits shows that the affidavits and medical literature submitted by HW&D raise a factual issue which is genuine and substantial and requires a hearing on the question of the existence of substantial evidence of effectiveness of Lutrexin.[2]

It is no answer to say, as the Government does, that FDA would be swamped with hearings beyond its capacity to cope, if a hearing were required in a case such as the instant one. The law as declared by the courts is that such difficulties do not excuse compliance with the statute or requirements of due process.

Moreover, the Government has made no showing that, in fact, FDA would be swamped by hearings, which would be limited to cases in which there was an issue of material fact as to the existence of substantial evidence of effectiveness. Each case must be decided on its merits and it seems evident that the Government is not in a position to accurately predict, or even estimate, the

[2] In our brief in No. 72-414 (Point II) we maintain that a hearing is also required on the jurisdictional questions arising under the Act as amended in 1962.

number of situations in which a hearing would be required.

The Government states that HW&D need make only a *prima facie* showing of the existence of substantial evidence; but then it proceeds to equate such a showing with an actual showing of substantial evidence. This was not the intent of Congress as the language of the statute and its legislative history demonstrate. On the contrary, the statute and its history show that the burden of proof in withdrawal-of-approval proceedings under Section 505(e)(3) is upon FDA itself. This is evident from a comparison of the provisions of Section 505 (b) and (d) (which place the burden of coming forward with convincing evidence of safety and effectiveness upon an *applicant* for an NDA), with the withdrawal provisions of Section 505(e).

4. We show, in Point IV, that HW&D was vested with the right to a hearing under the regulations in effect when HW&D accepted FDA's offer of a hearing and that this view is supported by the decisions of this Court. FDA failed to follow its own rules in such a case as this one. The substitution of the new regulations of May 8, 1970 cannot be made a basis for denying a hearing (even if HW&D were not entitled to a hearing under the new rules), under the holding of this Court in *Greene* v. *United States*, 376 U.S. 149 (1964) and the holding of the Sixth Circuit in *Upjohn* v. *Pennsylvania Railroad Company*, 381 F.2d 4 (1967).

ARGUMENT

The Government's Statement of the Question Presented

The Government's statement of the Question Presented is inaccurate. It assumes that HW&D has not submitted to the Commissioner "substantial evidence" of the effectiveness of Lutrexin and has therefore not complied with

the Commissioner's regulations of May 8, 1970 relating to hearings in a proceeding to withdraw approval of a new drug application (NDA).[3] One of the basic questions in this case is whether the evidence submitted by HW&D is "substantial" within the meaning of the statute and the Commissioner's regulations. For this reason we have rephrased the Question Presented as stated in the Government's brief (p. 2), and numbered it 1.

HW&D stated in its brief in opposition to the Government's petition for a writ of certiorari (p. 3) that, if the petition should be granted respondent would want to place two additional question before this Court which were argued in the Court below.

Accordingly, we have added two questions (numbers 2 and 3), as stated in our Memorandum in Opposition to the Government's petition for certiorari.

In its brief the Government expresses doubt whether the issues raised in numbers 2 and 3 of the Questions Presented are properly before this Court. It then proceeds to argue the merits of those issues (Br. 21; footnote 17, p. 24).

It is submitted that both questions 2 and 3 are "fairly comprised" within the basic question (No. 1) of whether HW&D is entitled to a hearing, within the meaning of the second sentence of this court's rule No. 40(d)(1). If, as we maintain, the statute requires a hearing in the instant case, it seems obvious that the validity of the Commissioner's hearing regulations of May 8, 1970 is called into question, even by the Question Presented as stated in the Government's brief. That Question, even as phrased by the Government, seems clearly to comprehend the question of whether due process requires a hearing in this case, regardless of whether the right to

[3] The regulations, as amended, appear at 21 CFR 130.12(a)(5) and 21 CFR 130.14 (J.A. 487-491).

the hearing arises under the statute, under the May 8, 1970 regulations, or under the regulations in effect when HW&D first requested a hearing.

Background

The Government notes that HW&D requested a hearing on April 18, 1969 and states that "Before the hearing could take place" the company, on August 19, 1969, filed suit in the United States District Court for the District of Maryland, seeking declaratory and injunctive relief from withdrawal of "approval" of the NDA for Lutrexin by FDA (Br. 6).

We are not certain of the reasons for this implication that a hearing would have been held had HW&D not filed the action in Baltimore.[4] It serves to recall, however, the fact that in its memorandum in support of its motion to dismiss in the Maryland case FDA *repeatedly* stressed that Congress intended that HW&D should have a hearing and that FDA was obligated to hold the hearing. For example, the Memorandum stated (p. 19):

> "Section 505 provides that an opportunity for a hearing be extended to an applicant before an approved NDA is revoked. When, as in the instant case, the applicant elects to proceed to hearing, *revocation of the NDA can be effected only after the Commissioner has, on the basis of the hearing record made certain statutory findings of fact. No alternate procedure for revocation is authorized by the Act.* (Emphasis supplied)."

That memorandum was filed in the latter part of October, 1969, *after* the first promulgation on September 19, 1969 of the regulations which defined "adequate and

[4] The rules then in effect required that the hearing commence within 90 days after acceptance of the opportunity to be heard unless the hearing examiner and the applicant otherwise agreed (21 CFR 130.14(b), revised as of January 1, 1969).

well-controlled" studies and established the criteria which must be met to obtain a hearing.[5] Thus, even after the regulations had been published, FDA was of the opinion that it was required to give HW&D a hearing. This had been the view of both industry and FDA since the enactment of Section 505. This view had not been changed by the 1962 Amendments to Section 505. Thus, in *In the Matter of Serc Tablets (Unimed, Inc.)*, Docket No. FDC-D-111 (1969), an NDA withdrawal proceeding in which FDA granted a hearing, the Government, by its attorneys, unequivocally recognized the right to a hearing and stated in a memorandum submitted to the hearing examiner some three months after HW&D had accepted its opportunity for a hearing:

> "When, as in the instant case, the applicant elects to proceed to a hearing, revocation of the NDA can be effected only after the Commissioner has on the basis of the hearing record made certain statutory findings of fact. *No alternate procedure for revocation is authorized by the Act* (Memorandum in Opposition to Respondent Unimed's Motion to Suspend the Hearing, pp. 8-10, emphasis supplied)."

These facts lend emphasis to the view that the real reason for the agency's present stance is the desire not to hold hearings because of the alleged multiplicity of hearings which might be required under the Act. This, in fact, is a principal argument of the Government and is discussed in Point IIIA of our argument, *infra*.

The report of the NAS-NRC Panel on Drugs Used in Disturbances of the Reproductive System stated that

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[5] The September 19, 1969 regulations were set aside because FDA failed to follow the procedural scheme of the statute. *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del. 1970). The present regulations of May 8, 1970 (J.A. 487-491) are the same as the September 19, 1969 regulations, insofar as here relevant.

Lutrexin was "possibly effective" for each claim made for the drug; that, in the case of the claim of effectiveness for dysmenorrhea, sound documentation was not available for evaluation; and that, in the case of the claims relating to premature labor and abortion, respectively, no document was "applicable" or available (J.A. 5).

It is clear that this report was a basic motivation, if not the principal one, for the FDA order withdrawing approval of the NDA for Lutrexin. In any event the opinion of the panel was the only information before FDA which suggested that Lutrexin was not effective.

In its petition for a writ of certiorari in this case (No. 72-394) the Government refers to "the mass of material" submitted to FDA by HW&D, declaring that "most of that material had previously been considered by the NAS-NRC panel" (Pet. 9), and thereafter stating that the NAS-NRC panel had "little difficulty" concluding that the studies submitted "did not meet the medical community's standard of adequacy" (Pet. 14).

In fact, only four of the fourteen studies (of which eleven were published) were considered by the NAS-NRC panel, *viz.*, two studies not identified by the panel by name, the study by G. E. Hayden, *Relief of Primary Dysmenorrhea* and that by S. S. Jones, *Lutrexin, A Drug For Relief Of Dysmenorrhea* (J.A. 7-8). None of the other studies (J.A. 86-172) was considered,* nor, of course, were the affidavits of experts which were subsequently furnished to the District Court in Baltimore and to FDA (J.A. 32-72).

It was therefore important to HW&D to inquire into the decision-making process which led to the withdrawal order. In response to inquiry by HW&D, dated August 18, 1969, the Acting Associate Director of Information

* Two of the studies were completed after the panel reported.

for Public Services of the Department of Health, Education and Welfare, replied, by letter of September 18, 1969 (J.A. 18-20), that neither FDA nor the Department has "any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel . . ."; that neither FDA nor the Department "has any statement, other than the reports themselves, reflecting the view of each member of the panel concerning the effectiveness of Lutrexin . . ."; [7] that "other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin . . . we do not know what medical or scientific literature was relied upon by the Panel"; and that FDA "has not conducted any independent clinical study or other scientific investigation of Lutrexin . . . at any time."

Thus, one of the principal supports of the FDA withdrawal order was formulated without the benefit of most of the available literature on Lutrexin and we do not know how or by what vote the panel reached its decision. Had the NAS-NRC panel had the benefit of such literature reflecting the conclusions that the clinical experts have reached, its evaluation might well have been that the drug is effective as claimed. The final evaluation of FDA might therefore have been entirely different. All that HW&D asks this Court, therefore, in this brief, is that the decision of the Fourth Circuit be affirmed so that the experts can be examined at a hearing to determine the validity and significance of their studies and of the opinions expressed in their affidavits. Certainly, more information should be made available on the manner in which the NAS-NRC panel reached its conclusions, particularly in the light of the statement of Dr. Allen, a member of the panel, that Lutrexin con-

[7] This point was important because, of the five members of the panel, only two were specialists in obstetrics and gynecology.

tains a biologically active component which has a relaxing effect on the uterus of laboratory animals and women and should remain on the market (J.A. 47, 48).

In *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F.2d 455 (D.C. Cir. 1972), as the Government states in its brief in the instant case, it was held that "the Commissioner may not simply rely on the reports of the NAS-NRC panels to call upon the holder of an NDA issued prior to October 10, 1962, to produce evidence of effectiveness establishing his right to a hearing or lose approval of the NDA." (Br. p. 32, footnote 32). The court thought that "it was incumbent upon the Commissioner . . . to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing"; and that, under Rule 56 of the Federal Rules of Civil Procedure (to which FDA has likened its regulations in 21 CFR 130.14) "the moving party has the burden of presenting evidence that establishes his right to summary judgment as a matter of law. . . ." 466 F.2d at 461.

FDA has presented no facts to show an alleged lack of substantial evidence of effectiveness. As we have stated, the sole "evidence" of lack of effectiveness is the opinion of the NAS-NRC panel that the drug is only "possibly effective." In the *USV* case above cited, the Court of Appeals characterized certain NAS-NRC panel reports as "cryptic and conclusory, without any statement of supporting facts." 466 F.2d at 461. The report on Lutrexin fits this description. All of the affirmative evidence before both the panel and FDA indicates that the drug is effective.[8] What FDA has done, therefore, is to place the burden of proving the existence of sub-

[8] Summary and explanation of the medical data is found in Point I, A and B, *infra*.

stantial evidence upon HW&D without even giving the Company an opportunity to be heard.

Under FDA's former regulations[9] which correctly followed the statute by granting hearings on NDA withdrawals, the burden of proof was on FDA to prove that there was a lack of substantial evidence of effectiveness for the drug involved. This is clear from *Bell* v. *Goddard*, 366 F.2d 177, 181 (7th Cir. 1966), which was decided some four years after enactment of the Drug Amendments of 1962.

Now, however, not only does the Government maintain that it is incumbent upon HW&D to show the existence of an issue of material fact but goes further and claims in effect that HW&D must show the existence of substantial evidence of effectiveness in order to obtain a hearing.

I

THE STUDIES AND AFFIDAVITS SUBMITTED BY HW&D IN ITS REQUEST FOR A HEARING RAISED GENUINE AND SUBSTANTIAL ISSUES OF FACT REQUIRING A HEARING.

Introduction

In *Hynson, Westcott and Dunning, Incorporated* v. *Finch*, (C.A. No. 21112, D. Md. 1970),[10] HW&D was prepared to offer factual proof at a trial, and is prepared to do so in a hearing before FDA, to support its contentions that Lutrexin is both safe and effective. This proof was and is available in the form of expert testimony by physicians who have studied and used Lutrexin

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[9] 21 CFR Section 130.14, revised as of January 1, 1969. These provisions were replaced by the present Section 130.14 in May, 1970.

[10] A summary of the Complaint in that cause appears at J.A. 15.

extensively, as well as in the form of medical investigations. The proper and legally required method of presenting such proof should have been at a trial or adjudicative hearing where the expert testimony could have been tested by cross-examination.

Unfortunately, however, this court does not have before it for review an order based upon any evidence adduced at a trial or hearing. The order is based upon a rejection by FDA of the evidence proffered by HW&D, in its renewed request for a hearing, dated October 16, 1970 (J.A. 24). The affidavits, studies, and other data, which will be summarized below, show that there exists solid evidence to support HW&D's claims of safety and effectiveness, evidence which clearly raises questions of fact which should be resolved in an adjudicative administrative hearing.

The effect of the failure to hold a hearing is two-fold: (1) the order before the court cannot be accorded the usual deference due to a determination by an expert administrative agency based upon substantial evidence adduced at a hearing; and (2) the court must itself determine the complex medical issues of fact before it, or as the Court of Appeals held, remand the case to the agency for determination after appropriate hearing.

A. Summary and Explanation of the Medical Data Relating to the Nature of the Product and Its Safety.

Lutrexin is indicated for use in the treatment of selected cases of premature labor, second and third trimester threatened abortion, and dysmenorrhea. The difference between abortion and premature labor is primarily one of the length of gestation. The term "abortion" or "threatened abortion" is generally used to refer to expulsion or threatened expulsion from the uterus of the product of conception before twenty weeks of the

pregnancy have passed; "premature labor" generally refers to the commencement of labor in the latter stage of the pregnancy but prior to term.

The term "dysmenorrhea" refers to the various symptomatic disorders suffered by some women during or just prior to menstruation, such as, cramps, backache, headache, nausea, vomiting, and malaise.

Premature labor, abortion, and dysmenorrhea are generally thought to result, at least in part, from abnormal or untimely contractions of the musculature of the uterus. The purpose of Lutrexin therapy is to quiet the uterus to prevent, in premature labor, a too-early birth, and in dysmenorrhea, to relieve cramping and associated symptoms.

(1) *The Product*

The active ingredient or uterine relaxing factor (URF) in Lutrexin is extracted from the corpus luteum of sow ovaries. The corpus luteum, in animals as well as human beings, is composed of cells formed after ovulation, i.e., after release of an egg from the ovary. In addition to the URF the corpus luteum secretes other hormones essential for the maintenance of pregnancy, including progestin (progesterone). It has been conclusively demonstrated, however, that the uterine relaxing factor or active ingredient in Lutrexin is a distinct entity whose quieting effect on the human uterus is not due to the presence of progesterone in the product (J.A. 148, 152-153; J.A. 153, 156).

(2) *Affidavits*

The safety of Lutrexin has not been questioned. Nor can it be. The affidavits of Doctors Bickers, Gratton, Majewski, Rezek, Gray and Trythall, the letter of Dr. Willard M. Allen,[11] as well as the medical studies set

[11] J.A. 32, 36, 39, 43, 54, 50, 47.

forth in the appendix (J.A. 86 *et seq.*), and discussed below, demonstrate conclusively that Lutrexin is safe.

Dr. Gratton, for example, states in his affidavit: ". . . there is no question that Lutrexin is safe, for I have administered up to 36,000 units of the drug to many patients in an eight to twenty-four hour period with no side effects to mother or child" (J.A. 37). Dr. Majewski has administered "4000 units of the drug stat., and 1000 units hourly thereafter until uterine contractions cease" with no side effect (J.A. 40-41). Dr. Rezek concludes to the same effect after prescribing "up to 12,000 units hourly for seven days" (J.A. 44-45). All told, Doctors Bickers, Majewski, Rezek, and Gratton have treated over two thousand patients with Lutrexin, with no side effects to patient or infant (J.A. 33, 40, 44, 36).

The expertise in obstetrics and gynecology of affiants Bickers, Gratton, Majewski, and Rezek is obvious from a reading of their affidavits and curricula vitae,[12] and needs no further elaboration. Their extensive study and use of Lutrexin also need not be restated. All state in their sworn affidavits that based upon their study of the literature on Lutrexin, described below, upon knowledge of the opinions of their expert colleagues, and upon their personal experience administering Lutrexin to several thousand patients, the product is safe.

(3) *Medical Literature*

Reports on Lutrexin have been made in the literature by Doctors Gratton, Majewski,[13] Rezek, Jones and Smith, Krantz, et al., Felton, et al., and S. Jones (J.A. 86, 92-111, 112-121, 160, 148, 153, 167).

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[12] J.A. 32 *et seq.*

[13] Dr. Gratton's paper and the 1968 paper of Dr. Majewski have not been published.

Krantz et al., in a study published in 1950 (J.A. 148), developed a laboratory method for showing the uterine-relaxing effect of aqueous extracts of corpus luteum in live guinea pigs. This method is important, for it forms the basis for the establishment of a standard unit of dosage for the uterine relaxant activity of Lutrexin. The method is a simple one: the guinea pig is treated with a hormone to induce an artificial state of pregnancy. The uterus of a guinea pig so treated demonstrates a regular pattern of contractions. To measure this activity, and the effect of an injection of lututrin (the active ingredient of Lutrexin), the pig is anesthetized, its uterus is lifted partially out of the abdomen and attached to a lever, which records the level of contractions.

In the study, Krantz et al. injected an aqueous corpus luteum extract into the jugular veins of seventeen guinea pigs prepared as stated above. The recordings of uterine contractions showed a marked reduction in uterine activity in all of the animals injected. As a result of the work of Krantz et al., it was possible to establish a standard unit of URF activity: the minimal amount which, when injected intravenously into the hormone-treated guinea pig, effects a 90 per cent reduction in the height of spontaneous uterine contractions for a period of ten minutes.[14] Thus, the clinician is provided with a standardized unit of Lutrexin, which permits him to administer a "known" amount to his patients. He can then adjust the dosage according to clinical response of the patient.

The published studies of Rezek, and Jones and Smith demonstrate the safety of Lutrexin in the treatment of dysmenorrhea in women. Dr. Rezek treated a total of 298 dysmenorrheic patients with substantial doses of Lutrexin and "no undesirable by-effects of any kind were

[14] See papers by Felton et al. and Jones and Smith, J.A. 153, 160.

noticed, although some patients were observed for as long as eleven periods" (J.A. 112, 117). Jones and Smith treated 90 dysmenorrheic women with Lutrexin, and in addition gave large doses to 10 men to test the toxicity of Lutrexin:

> "In testing the toxicity of the drug, as much as 10,000 units in a single dose was given to 10 men with no untoward results. Two women under observation have also taken 10,000 units at one time and, although they were somewhat drowsy for several hours, no other effects were observed" (J.A. 160, 162).

The reports of Gratton, Majewski, Rezek, Gray, and Trythall involve treatment of over four hundred pregnant women with Lutrexin, with no reported side effects (J.A. 87, 92-111, 112, 131, 135).

On the basis of the foregoing studies published in the medical literature, and on their own experience and discussions with colleagues, Doctors Bickers, Gratton, Majewski, and Rezek concluded in their affidavits that Lutrexin is safe for use in treatment of premature labor (and abortion) and dysmenorrhea.

To date, the FDA has offered no refutation of the evidence proffered by HW&D on the question of the safety of Lutrexin.

B. Summary and Explanation of the Medical Data Relating to the Effectiveness of the Product.

(1) *Affidavits*

Doctors Bickers, Gratton, Majewski, Rezek, Trythall and Gray state in their affidavits that, based upon their study of the medical literature on Lutrexin, reviewed below, upon their own study and use of Lutrexin, and upon knowledge of opinions of their colleagues, Lutrexin is effective for use in the treatment of second and third

trimester threatened and habitual abortion and premature labor (J.A. 34, 37, 40, 44, 51, 55). Doctors Bickers and Rezek, upon the same basis, state in their affidavits that Lutrexin is effective for use in the treatment of dysmenorrhea (J.A. 34, 44).

All affiants have had extensive experience in the use of Lutrexin: Doctors Bickers, Gratton, Rezek, Majewski, Gray, and Trythall have used Lutrexin in treatment of pregnancy problems for an average of 14 years, involving over 2,000 patients; Doctors Bickers and Rezek have used Lutrexin in treatment of 1,500 dysmenorrheic patients for over 15 years.

It is submitted that based upon the affidavits alone, HW&D demonstrated in its request for a hearing after dismissal of its action in the Maryland District Court the existence of genuine and substantial issues of fact requiring a hearing. The Commissioner's bare statement that the affidavits cannot be accepted because of a failure to identify adequate and well-controlled investigations (J.A. 74) is controverted by statements in the affidavits. Thus, Dr. Gratton stated in his affidavit:

> "Studies such as the one reported in Exhibit B [J.A. 87], utilizing the past histories of the patients as controls . . . are proof of the effectiveness of Lutrexin. Such studies . . . cannot be dismissed on the ground that they are valueless because they do not use a double-blind placebo type of investigation. The latter type of investigation is inconceivable from the standpoint of ethics and morality where, as here, there exists a high risk of mortality and the physician is testing a drug (Lutrexin) which is clinically-proven to be effective" (J.A. 37).

Similarly, Dr. Majewski stated in his affidavit:

> "The method of investigation utilized in my studies (Exhibit B, C, and D) [J.A. 92-111] *viz.*, use of the patients as their own controls, or use as a control of

statistics reflecting the experience with other patients with no treatment, together with the general clinical experience of the physician, constitute the only humane approach to the study of the effectiveness of a drug for use in threatened abortion and premature labor. These complications of pregnancy carry a high risk to the life of the fetus and perhaps the mother. Use under such conditions of a double-blind, placebo type of investigation would be unethical and immoral, where, as here, there exists a drug (Lutrexin) clinically-proven to be of value in the treatment of the affliction involved" (J.A. 41).

(2) *Medical Literature*

(a) *Historical Controls*

FDA's regulations defining "adequate and well-controlled studies" require that a medical investigation contain a method of selection of the subjects that . . . provides a comparison of the results of treatment . . . [using the drug under investigation] with a control in such a fashion as to permit quantitative evaluation" (21 C.F.R. 130.12(a)(5)(ii)(a)(4); J.A. 488). One method of control acceptable to the agency is historical control:

> "Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen . . . the effectiveness of which is established" (21 C.F.R. 130.12(a)(5)(ii)(a)(4)(iv); J.A. 488-489).

It cannot be gainsaid that premature labor and threatened and habitual abortion are conditions involving a "high and predictable mortality" as well as conditions "where morbidity is predictable." If premature contractions of a gravid uterus are not halted, a dead fetus is almost certain.

The necessity of performing certain tests using historical controls is described by Dr. Allen who was a member of the NAS/NRC panel which reviewed Lutrexin.[15]

> "There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so 'sacred' that any other type is often not recognized as investigative. However, there are many clinical problems in which this type of study violates the rules of clinical morality as

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[15] Dr. Allen also is on record in support of the continued marketing of Lutrexin. He has stated, in a notarized letter to HW&D:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of laboratory animals and women". * * * "The clinical evidence which you have submitted [to me] . . . does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective." * * * "Lutrexin, since it contains an active principal which relaxes the uterus, should be available for the treatment of premature labor . . ." J.A. 47, 48.

well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less." [16]

(b) *HW&D's Investigations*

In Dr. Gratton's study,[17] which involved habitual aborters, the patients were used as their own controls, and the results of Lutrexin treatment vis a vis prior untreated pregnancies were statistically evaluated:

". . . in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001. Probabilities ranging from .001 to .05 were observed in women with one to five pregnancies who had been treated with Lutrexin" (J.A. 88).

In Dr. Majewski's first two studies,[18] which involved premature labor, the results were compared with the documented history of premature births in the hospital where the study was performed:

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[16] J.A. 121, 127-128. This paper is not a report on Lutrexin.

[17] J.A. 86.

[18] J.A. 92, 99.

"The hospital wherein the study was conducted has . . . a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries, for a percentage of 9.4. In our series of patients using the uterine relaxing factor [Lutrexin] the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent), a saving of 21 premature deliveries" (J.A. 94).

In Dr. Majewski's second study,[19] which is a continuation of the first study, the comparison was enlarged to one of the total number of premature survivals, stillbirths and neonatal deaths during the 15-month period the study was in progress. In Dr. Majewski's third study the results were compared statistically with the results of prior untreated pregnancies (J.A. 106).

The studies by Drs. Rezek, G. Jones et al., and S. Jones show the clinical effectiveness of Lutrexin (J.A. 112, 160, 167). The studies of Drs. Rezek and G. Jones present laboratory confirmation of the biological activity of Lutrexin in humans (J.A. 116, 162-163).

It is clear from the foregoing summary of the affidavits and studies submitted in HW&D's request for a hearing and from the Commissioner's factual criticisms of the affidavits and studies (J.A. 72)[20] that genuine

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[19] J.A. 99.

[20] We have shown in detail in our brief in No. 414 (pp. 33-35) that FDA's critique of the studies and affidavits, as held by the Court below, ". . . at most, . . . merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (J.A. 180).

and substantial issues of disputed fact exist that require a hearing. As clearly appears from the above summary, HW&D's evidentiary showing cannot be dismissed as being merely "testimonial" in nature.

II

FDA'S "SUMMARY JUDGMENT" REGULATIONS ARE INHERENTLY UNFAIR AND AS APPLIED IN THE INSTANT CASE DENIED HW&D DUE PROCESS OF LAW.

A. The Regulations

A proceeding under FDA's "summary judgment" regulations (J.A. 490-491) is initiated by a notice from the Commissioner of an opportunity for a hearing on a proposal to withdraw approval of an NDA under Section 505(e) of the Act (J.A. 479). The regulations require a manufacturer responding to such a notice to submit a request setting forth ". . . specific facts showing that there is a genuine and substantial issue of fact that requires a hearing" (J.A. 491). The request must identify "adequate and well-controlled clinical investigations" to support claims of effectiveness for the drug (J.A. 491). If the Commissioner determines that the request does not identify any such studies, he will deny the request for a hearing because the request did not show that there is "a genuine and substantial issue of fact" that requires a hearing.

The regulations are unfair on their face. They do not provide for the submission by or on behalf of the Commissioner of any evidence to rebut the manufacturer's data or to show that no genuine and substantial issue of fact exists. They do not provide the manufacturer an opportunity to refute the Commissioner's findings that the medical studies submitted in the request for a

hearing are not adequate and well-controlled and do not raise a genuine and substantial issue of fact requiring a hearing. Finally, no attempt is made in the regulations to provide for a separation of the prosecutorial and judging functions of the Commissioner.

B. Decision Of The Court Of Appeals.

The Government states in its brief that the Court of Appeals upheld the validity of the Commissioner's "summary judgment" regulations (Br. 24, 30, 33 (n. 23)). More accurately, the Court held that while it may be assumed that the regulations may be applicable to this case, the Commissioner's application of them to deny HW&D a hearing was arbitrary and not in conformity with due process and the Administrative Procedure Act (J.A. 177-179). Thus, the court said:

> ". . . we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn" (J.A. 179).

The Court held that the Commissioner's criticisms in his withdrawal order of HW&D's medical studies indicate that disputed issues of fact exist requiring a hearing:

> "Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper

evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into" (J.A. 180).

C. The Unfairness of the "Summary Judgment" Regulations.

FDA has characterized its procedural regulations governing hearings under Section 505 of the Act as ". . . similar in some respects to a trial court's granting of a motion for summary judgment when there are no legally relevant controverted facts to be decided" (Br. 20-21). The only similarity between FDA's procedure and that contemplated by Rule 56 of the Federal Rules of Civil Procedure is the concept of the requirement of a genuine and substantial issue of fact as a condition for an adjudicative hearing. None of the safeguards carefully elaborated by rulings of this and lower federal courts in Rule 56 decisions has been incorporated into FDA's procedures.

(1) *Lack Of An Impartial Decision-Maker*

A fundamental requirement of due process in administrative proceedings is an "impartial decision maker." *Goldberg* v. *Kelly*, 397 U.S. 254, 271 (1970); *Wong Yang Sung* v. *McGrath*, 339 U.S. 33, 41-45 (1950). This requirement was clearly not met in the administrative proceedings before FDA. Nor, as presently constituted, do the regulations meet it. (21 CFR 130.14; J.A. 490). Under the regulations, the Commissioner, acting in effect as a party litigant or advocate, moves for a summary disposition of the NDA withdrawal proceeding by issuing a notice of an opportunity for a hearing. In the

notice, in this case, the Commissioner stated that the information before him "does not provide substantial evidence of effectiveness of . . . [Lutrexin] for its recommended uses" (J.A. 12) and that if a final order were issued withdrawing NDA approval, the drug ". . . would be subject to regulatory proceedings" (J.A. 13). After submission of HW&D's request for a hearing, with attached medical data in support thereof, the Commissioner-advocate judges whether the submission raises a genuine and substantial issue of fact requiring a trial-type hearing. This commingling of the functions of prosecutor and judge is patently unfair. As stated in the Report of the President's Committee on Administrative Management, quoted favorably in *Wong Yang Sung*, supra at 42:

> "This not only undermines judicial fairness; it weakens public confidence in that fairness. . . . [D]ecisions affecting private rights and conduct lie under the suspicion of being rationalizations of the preliminary findings which the . . . [agency], in the role of prosecutor, presented to itself" (Administrative Management in the Government of the United States, Report of the President's Committee on Administrative Management, 36-37 (1937)).

The Government cites in its brief in support of its hearing procedures the practice of the Federal Trade Commission and the National Labor Relations Board in this regard, stating that their procedures are "similar" to FDA's (Br. 23).[21] The procedures of those agencies relating to motions for summary judgment are, in fact, dissimilar to FDA's for they provide for the very safeguard we have shown to be missing in the FDA procedures, *viz.*, an impartial decision-maker whose sole role is to judge (16 CFR 3.24; 29 CFR 102.24, 102.25). The

[21] The Administrative Conference recommendation referred to in the Government's brief (p. 23) was that summary judgment procedures similar to Rule 56 of the Federal Rules of Civil Procedure be adopted. This FDA has not done.

trial examiner in such cases receives evidence from counsel for the agency and the private party on the question of whether disputed facts exist, and renders an impartial decision thereon. The procedures adopted by the FTC and NLRB are the type contemplated by the Administrative Procedure Act. The Final Report of the Attorney General's Committee on Administrative Procedure states in part:

> "These types of commingling of functions of investigation or advocacy with the function of deciding are thus plainly undesirable. But they are also avoidable and should be avoided by appropriate internal division of labor. For the disqualifications produced by investigation or advocacy are personal psychological ones which result from engaging in those types of activity; and the problem is simply one of isolating those who engage in the activity. Creation of independent hearing commissioners insulated from all phases of a case other than hearing and deciding will, the Committee believes, go far toward solving this problem at the level of the initial hearing provided the proper safeguards are established to assure the insulation. * * *" Rep. Atty. Gen. Comm. Ad. Proc. 56 (1941), S. Doc. No. 8, 77th Cong., 1st Sess. 56 (1941).

The Government's constant refrain that its summary disposition regulations are essential in order to enable the agency to carry out the functions mandated to it by Congress cannot serve to justify dispensing with impartial decision making. As this court stated in applying the separation of functions requirement of the Administrative Procedure Act to proceedings before the Immigration Service:

> "Nor can we accord any weight to the argument that to apply the Act to such hearings will cause inconvenience and added expense to the Immigration Service. Of course it will, as it will to nearly

> every agency to which it is applied. But the power of the purse belongs to Congress, and Congress has determined that the price for greater fairness is not too high. The agencies, unlike the aliens, have ready and persuasive access to the legislative ear and if error is made by including them, relief from Congress is a simple matter" (*Wong Yang Sung, supra* at 46-47).

The Court of Appeals for the District of Columbia Circuit in a recent decision reviewed an order of the Commissioner withdrawing approval of the NDA for a drug pursuant to the "summary judgment" regulations. The court stated:

> "The Commissioner acted pursuant to 21 C.F.R. § 130.14, the regulation establishing a summary judgment procedure for the Food and Drug Administration. This regulation is modeled after Rule 56 . . . A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the contentions of opposing parties, but was himself the moving party undertaking to support his own proposed order" *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare,* 466 F.2d 455, 461 (1972).

(2) *Burden of Proof in Summary Judgment Proceedings*

We show under Point III that the burden of proof in withdrawal proceedings pursuant to section 505(e) of the Act is on the Commissioner. It is also settled beyond peradventure that the party moving for summary judgment has the burden of ". . . showing the absence of a genuine issue as to any material fact . . ." *Adickes* v. *S. H. Kress and Company,* 398 U.S. 144, 157 (1970). Under FDA's regulations, the Commissioner has no burden of showing the absence of disputed facts; rather the party opposing the motion for summary judgment has the burden of proving the existence of a genuine issue

of fact. This is a clear perversion of the concept of summary judgment.

This court has outlined the conditions under which a movant is entitled to a grant of his motion for summary judgment:

> ". . . Rule 56 authorizes summary judgment only where the moving party is entitled to judgment as a matter of law, where it is quite clear what the truth is, . . . no genuine issue remains for trial . . . the purpose of the rule is not to cut litigants off from their right of trial by jury if they really have issues to try." *Sartor* v. *Arkansas Natural Gas Corp.*, 321 U.S. 620, 627 (1944).

The Commissioner acting under his form of summary judgment met none of these conditions. Indeed, since the Commissioner contented himself with merely a criticism of HW&D's medical studies and affidavits, and did not submit evidence showing the absence of a genuine issue of fact, HW&D was entitled to judgment as a matter of law (or at the least a hearing). The Commissioner's burden was well-described by the Court of Appeals for the District of Columbia Circuit:

> "The petitioner's applications had been approved, pursuant to 21 U.S.C.A. § 355(b) (1961), but now, under 21 U.S.C. § 355(e), the Commissioner proposed, without a hearing, to withdraw that approval on the basis of a new standard and new information, together with the evidence available when approval was originally granted. In this situation we think it was incumbent upon the Commissioner, before calling upon the petitioner for additional evidence establishing a right to a hearing, to state *facts* and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing. This view of the Commissioner's burden is consistent with the prac-

tice under Rule 56 of the Federal Rules of Civil Procedure. *Under that rule the moving party has the burden of presenting evidence that establishes right to summary judgment as a matter of law*; and he may not, by the bare assertion that he is entitled to summary judgment, shift to his opponent the burden of establishing the contrary" (Emphasis supplied). *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare*, 466 F.2d 455, 461 (1972).

D. Due Process.

The Court of Appeals held that denial of a hearing to HW&D was contrary to applicable principles of due process and the Administrative Procedure Act and to a reasonable construction of the Commissioner's own regulations (J.A. 179).

This holding follows the decisions of the Supreme Court in *Goldberg* v. *Kelly*, 397 U.S. 254 (1970) and *ICC* v. *Louisville & N.R. Co.*, 227 U.S. 88 (1913). As stated by Mr. Justice Brennan in *Kelly* "In almost every setting where important decisions turn on questions of fact, due process requires an opportunity to confront and cross-examine witnesses" (397 U.S. at 269). The decision below and our analysis of the evidence submitted by HW&D (Point I) demonstrate the applicability of these cases here. We have already shown in the brief for Cross-petitioner in No. 72-414, that such cases require a hearing on the jurisdictional questions (Brief for Cross-Petitioner pp. 31-38).

Likewise, the facts at issue here (in No. 72-394) are adjudicative facts, just as are those involved in the jurisdictional questions, i.e. "those to which the law is applied in the process of adjudication. . . . They relate to the parties, their activities, their properties, their business." 3 Davis, Administrative Law Treatise, § 15.03,

p. 353. They are thus distinguished from legislative facts which are those upon the basis of which law and policy have been previously established.

The question of whether the materials submitted by HW&D constitute "substantial evidence" as defined in Section 505(d) of the Act can only be determined upon the basis of a trial-type hearing. Davis, Administrative Law Treatise, 1970 Supplement, Sections 7.01, 7.04. They relate only to the business of Hynson, Westcott & Dunning in the marketing of Lutrexin, and to its labeling, and are not pertinent to any other drugs or their status under the Act. Professor Davis' view is entirely consistent with the decisions of this Court in *Kelly* and *Louisville & N.R. Co., supra.*

III

RESPONDENT HW&D IS ENTITLED BY LAW TO AN EVIDENTIARY, TRIAL-TYPE HEARING UPON THE QUESTION OF WHETHER THERE IS SUBSTANTIAL EVIDENCE OF THE EFFECTIVENESS OF LUTREXIN.

A. The Hearing Requirement Of The Statute And The Alleged Incapacity Of The Agency To Meet Anticipated Demands For Hearings If It Is Enforced.

The Government repeatedly sounds the alarm that, if FDA were required to provide HW&D a hearing the agency would have to grant a hearing before withdrawing approval for each of the some 3500 products reviewed by the panels of the National Academy of Sciences-National Research Council (NAS-NRC) and that "the agency would be mired in hearings for years" (Br. 19). The same theme recurs in the Government's brief in *Bentex.*[22]

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[22] *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555 (J.A. 270), one of the cases consolidated with the instant case (No. 72-394).

We do not maintain that a hearing would be required in every such case, even under the old regulations which were superseded by the so-called "summary judgment" regulations of May 8, 1970.

Thus, a hearing is not required where, even if petitioner's contentions were proved, it would avail him nothing because the legality of the order attacked would not be effected. *Dyestuffs & Chemicals, Inc.* v. *Flemming*, 271 F.2d 281 (8th Cir., 1959), cert denied, 362 U.S. 911 (1960). Nor is a hearing required where no fact question is involved. *Sun Oil Co.* v. *FPC*, 256 F.2d 233 (5th Cir., 1958), cert denied, 358 U.S. 872. This is obviously not true of HW&D's contentions here, as we show under Point I. The affidavits and medical literature submitted to the Commissioner are, at the least, sufficient to raise an issue of material fact on the question of substantial evidence, as the Court of Appeals held.

We do not know in how many of the cases involved, a hearing would be required since each case must be evaluated on its own facts. We know, however, that no hearing has been held to date under the 1970 "summary judgment" regulations and it seems apparent that the Commissioner intends to grant such hearings only in extraordinary situations, if this Court sustains the 1970 restrictive regulations (21 CFR 130.14, J.A. 490-491). The Government states, in Footnote 15 of its brief in the instant case (No. 72-394) that:

> "The nature of the problems is such that formal hearings are not likely to be needed in many instances. If studies exist that appear on their face to constitute adequate and well-controlled investigations as defined in the regulations, the Commissioner would, in the absence of unusual circumstances, find the drug effective and not pursue withdrawal of its NDA. If the manufacturer is unable to make a

prima facie showing that such studies exist, a hearing would be useless" (Br. p. 20).

Thus, FDA in effect equates the concept of *prima facie* showing with a showing of substantial evidence; conversely, it equates the statutory concept of "lack of substantial evidence with its idea of a lack of a *prima facie* showing." Obviously, if this approach is legally justifiable, a hearing would rarely be required and the merits of each case could be tried *ex parte*, on motion, as FDA has done in the instant case. But this was clearly not the intent of Congress. It is not supported by the language of the statute itself or its legislative history.

In passing upon an NDA the Secretary (Commissioner) is required, under Section 505(c), (21 U.S.C. 355(c)), either (1) to approve the application or "(2) give the applicant notice of an opportunity for a hearing. If the applicant elects to accept the opportunity for a hearing by written request within thirty days after such notice, *such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree*" (emphasis supplied).

It seems perfectly apparent that under such an explicit provision the Commissioner may not avoid a hearing simply by deciding *ex parte* that there is is a lack of substantial evidence of effectiveness.

Certainly, there is no sound reason for saying that the right to a hearing in a withdrawal proceeding under Section 505(e)(3) is any less firm than under Section 505(c)(2), above quoted in part. Senator Eastland, the Chairman of the Senate Committee on the Judiciary, in explaining to the Senate the withdrawal provision of S.1552, as finally enacted, stated:

"Withdrawal of approval of any new drug application on the basis of the foregoing grounds would

be preceded by a hearing and an order with findings on the basis of the record." [23]

One of the "foregoing grounds" referred to by Senator Eastland is that upon the basis of which FDA acted in the instant case (Section 505(e)(3)).

Even if, because of staff or financial limitations, FDA could not handle expeditiously the case load of NDA withdrawal proceedings where hearings are required by the statute, that would constitute no valid reason for denying such hearings. Section 505(e) of the Act directs the Commissioner to give due notice and opportunity for hearing prior to withdrawal of approval of an NDA. FDA's position herein would, in effect, read this provision out of the statute. This court has repeatedly held that the authority of an administrative agency is circumscribed by the powers granted to it by Congress.

Thus, in *Manhattan General Equipment Co.* v. *Commissioner of Internal Revenue*, 297 U.S. 129, 134 (1936) the court said:

> "The power of an administrative officer or board to administer a federal statute and to prescribe rules and regulations to that end is not the power to make law, for no such power can be delegated by Congress, but the power to adopt regulations to carry into effect the will of Congress as expressed by the statute. A regulation which does not do this, but operates to create a rule out of harmony with the statute, is a mere nullity. * * *

This statement was quoted with approval in *Dixon* v. *United States*, 381 U.S. 68, 74 (1965).

In *Stark* v. *Wickard*, 321 U.S. 288, 309 (1944) the court said:

> "When Congress passes an Act empowering administrative agencies to carry on governmental activities,

[23] 108 Cong. Rec. 16,304, August 23, 1962.

> the power of those agencies is circumscribed by the authority granted."

The Food and Drug Administration itself was admonished in *62 Cases etc.* v. *United States*, 340 U.S. 593, 600 (1951), that:

> "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop."

Unless, therefore, there is no issue of material fact raised by the evidence submitted in a withdrawal proceeding under Section 505(e), the Commissioner may not deny a hearing under the statute. The contention that FDA could not hold all the hearings which would be necessary if Congress' directions were followed is no excuse, even if true.

The Court addressed itself to this point in *Ohio Bell Telephone Co.* v. *Public Utilities Commission of Ohio*, 301 U.S. 292, 305 (1937) when it said, per Mr. Justice Cardozo, with reference to the failure of the Commission to honor the requirement of a hearing:

> "There can be no compromise on the footing of convenience or expediency, or because of a natural desire to be rid of harassing delay, when that minimal requirement has been neglected or ignored."

We quote elsewhere the opinion of this court in *Wong Yang Sung* v. *McGrath*, 339 U.S. 33, 46-47 (1950), that the argument that application of the Administrative Procedure Act to immigration hearings will cause inconvenience and added expense to the Immigration Service, cannot be accorded any weight; that Congress has determined that the price of greater fairness is not too high; that the agencies have access to Congress; and if error has been made, Congress can correct it. Congress later

exempted the Service from the APA and it can modify the hearing requirements of Section 505 if it so desires.

The Court of Appeals for the Third Circuit, in a situation where the Federal Power Commission rejected proposed tariff changes without a hearing required by statute, declared:

> "We can understand, as the argument in this case has seemed to imply, that the Commission may have had to contemplate serious injury to the public interest because of its inability with very limited funds and staff to perform the enormous task of investigation and analysis imposed upon it in times when so many public utilities are submitting important proposals within its jurisdiction and the statutory scheme requires it to act promptly or let proposals go by default. But the remedy lies with Congress. If changes in the law are needed, or more personnel to administer existing law, or both, it is not for the administrative agency or the courts to try to make up for this deficiency by taking unauthorized short cuts or indulging time saving procedures which fail to accord parties the rights which the law as written gives them. Viewed in most favorable light, that seems to us to be what the Commission has tried to do here. It follows that the order of May 29 must be set aside as wholly beyond the authority of the Commission." *Mississippi River Fuel Corp.* v. *Federal Power Com'n*, 202 F.2d 899, 902-903 (1953), appeal dismissed, 345 U.S. 988.

It is not our position that a denial of a hearing, either under a rule or in an individual case, if a hearing is not required by statute, is unrelated to "a vast proliferation of hearings" by which the processes of regulation would be "prolonged" or "crippled". *FPC* v. *Texaco, Inc.*, 377 U.S. 33, 44, (1964). We say only that where the statute mandates a hearing it may not be denied in an individual case on the ground that administrative inconvenience or even such "a vast proliferation" will occur.

In the new drug situation with which we are dealing there is before the court only the unsubstantiated statement of the Government that such a vast proliferation would ensue. It is our contention (See Point I) that HW&D has submitted evidence to FDA which raises a substantial and material issue of fact and that, as the Fourth Circuit thought, a hearing is required to determine whether there is, in fact, substantial evidence of the effectiveness of Lutrexin. This evidence, we submit, even brings the case within the regulation upon which the Government relies to deny a hearing.

B. The Burden of Proof in Withdrawal Proceedings

The Government refers to *Ubiotica Corporation* v. *Food & Drug Administration*, 427 F.2d 376, 378 (6th Cir. 1970), which held that, by Section 505 of the Act the Congress clearly placed upon the applicant for an NDA the burden of showing that the drug which it proposes to distribute in interstate commerce is both safe and effective for its intended use.

But that is not the situation here. Here there is an attempt to place the burden of proof, not upon an *applicant* for an NDA, but upon one whose NDA became effective in 1953, the alleged approval of which FDA seeks to withdraw.[24]

It is significant, moreover, and the Court observed in *Ubiotica*, that "the Government came forward with proof as to why petitioner had not satisfied the burden of proof required of a new drug applicant under Section 355"

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[24] We maintain in our Brief in No. 72-414 that, the NDA for Lutrexin was not "deemed approved" under Section 107(c)(2) of the Drug Amendments and is, therefore, not subject to withdrawal of approval proceedings. Obviously it was not actually approved because approval of NDA's was not instituted until the enactment of the 1962 Amendments.

(427 F.2d at 378). It even introduced a "double-blind" study to show the ineffectiveness of the drugs in question. The hearing, affording cross-examination of Government witnesses, and the evidence introduced in that case, as shown by the Court's opinion, stand in sharp contrast to the summary treatment which FDA has given the studies by eminent specialists in the Lutrexin matter.

The structure of Section 505(e), providing for withdrawal of approval of NDAs, clearly contemplates that the burden of showing compliance with the statutory conditions for revocation is upon FDA.

One of the grounds of withdrawal is new evidence that the drug is not safe (Section 505(e)(2)). Surely the Commissioner may not make the finding required without producing such new evidence as the basis for the required finding. Under Section 505(e)(4) approval of an application may be withdrawn if the Commissioner finds "that the application contains any untrue statement of a material fact." It seems inconceivable that approval of an application could be withdrawn on this ground without the production by the Commissioner of the evidence that the applicant's statement was untrue. Likewise, under Section 505(e)(3) approval of an NDA may be withdrawn "on the basis of new information before [the Commissioner] with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . ." The only way to show that the evidence submitted by HW&D on Lutrexin is not substantial is for FDA to introduce countervailing evidence.

These and each of the several other bases for withdrawal of approval of NDA's are also conditioned upon

"due notice and opportunity for a hearing to the applicant." We have already noted that the statute itself and its legislative history contemplate an actual hearing (except, of course, where there is no fact question involved).

It seems clear, therefore, that the application of the May, 1970 regulations in such a manner as to shift the burden of proof from FDA to HW&D flouts the statutory mandate.

The proponent of an order approving an NDA is the applicant. The proponent of an order withdrawing approval is the Commissioner. In the latter situation Section 7(c) of the Administrative Procedure Act provides (5 U.S.C. 556(d)) that:

> "Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof."

Since the Food, Drug and Cosmetic Act does not otherwise provide, Section 7(c) is applicable and it is evident that by reason of that Section alone, the burden is on the Commissioner in a withdrawal of approval proceeding.

This means, according to the Court of Appeals of the District of Columbia that it was incumbent upon the Commissioner "to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing" (*USV Pharmaceutical Corporation* v. *Secretary of Health, Education & Welfare*, 466 F.2d at 461).

". . . It is the general rule that . . . 'the burden of proof lies upon him who affirms, not him who denies' ". *National Motor Freight Traffic Association, Inc.* v. *United States*, 242 F. Supp. 601, 605 (D.D.C. 1965).

C. FDA's "Summary Judgment" Regulations Viewed in the Light of the Structure of Section 505.

FDA relies on decisions in the sixth and second circuits[25] and on a decision in the district court in the third circuit[26] to support the validity of its hearing procedures. For the reasons set forth below, we submit that those courts erred and their decisions should not be followed by this court.

The review provisions of Section 505, 21 USC 355, are so structured as to make it clear that Congress intended a hearing on proposals to withdraw NDAs if the applicant requests a hearing. Thus, Section 505(e), 21 USC 355(e), provides: "The Secretary shall, after due notice and opportunity for a hearing" withdraw approval of an NDA if he makes the requisite statutory findings. The appeal provision (Section 505(h), 21 USC 355(h)) states that "The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive", and that, upon a proper showing, the reviewing court may grant a request "for leave to adduce additional evidence" before the agency:

> "The court may order such additional evidence to be taken by the Secretary and to be adduced *upon the hearing* in such manner . . . as to the court may seem proper" (Emphasis supplied).

A reading of these provisions leads one ineluctably to the conclusion that Congress deliberately intended to require an evidentiary hearing prior to withdrawal of an NDA. If this were not the case, the use of the terms quoted above would be meaningless. That this is so is apparent in the case at bar. Thus, there is not "substantial evidence" upon which the finding of the Secre-

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[25] *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970).

[26] *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).

tary can be based, for no such evidence was adduced at a hearing, and therefore, the findings of FDA in this case can hardly be considered conclusive. Similarly, the phrases in Section 505(h) "adduce additional evidence" and "order such additional evidence be taken" and "to be adduced" make little sense in a case before the appellate court based upon an order entered without a hearing.[27]

The opinions in *Upjohn*, *Pfizer*, and *Pharmaceutical Manufacturers Association*, *supra*, did not analyze the framework of Section 505 in upholding FDA's regulations. For this reason alone, this court should not follow those decisions.

A proffer of evidence of the caliber described in Point I, *supra*, is a sufficient showing that a hearing is warranted in this case. Contrary to FDA's position, Congress clearly intended that a hearing be held under these circumstances. As we show in the Argument, *supra*, under Background, FDA thought so too as late as the latter part of October, 1969.

D. Additional Contentions of the Government

The Government states that "the Court of Appeals did not find that any of the Commissioner's conclusions were unreasonable, erroneous, or arbitrary, but simply ordered a hearing because something might come out at such a hearing that would show that the studies were not as defective as they appeared to be on their face" (Br. 13). On the contrary, the Court's discussion of the Commissioner's action clearly reflected its view that the action was arbitrary and unreasonable. Moreover, the

[27] Where only a question of legal interpretation is involved, the Court of Appeals would not be dependent upon findings supported by substantial evidence and could, therefore, render a decision.

Court concluded that the objections raised by the Commissioner "do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin; . . . at most, they merely create a genuine issue of fact to be resolved at a hearing upon proper evidence" (J.A. 180).

As it did in its petition for a writ of certiorari, the Government again cites *United States* v. *Storer Broadcasting Company*, 351 U.S. 192 (1956) and *Federal Power Commission* v. *Texaco*, 377 U.S. 33 (1964) in support of its argument that the May 8, 1970 regulations, as applied to deny HW&D a hearing, are valid rules. (Br. 22-23). But, as we pointed out in our brief in opposition to the petition, in those cases there was no factual issue upon which to hold a hearing. It was either conceded or obvious that the applications to the agencies failed to conform to the rules involved. That is certainly not true here, as the Fourth Circuit held.

The Government states that "the Courts of Appeals have similarly declined to insist upon the holding of hearings when there are no material issues of fact to be resolved," citing cases (Br. 23). We hope we have made it clear that we interpret the opinion of the Court of Appeals as holding that issues of material fact have, indeed, been raised by the evidence presented to FDA by HW&D. It is our position, as it was the position of the Court of Appeals, that the Commissioner has construed the definition of substantial evidence in Section 505 in too narrow a manner.

The Government states:

> "Nearly 6,000 of the 16,500 claims evaluated by NAS-NRC received 'possibly effective' ratings (see n. 13, *supra*, and accompanying text), and if such a rating entitles the manufacturer to an evidentiary

hearing, FDA would be obliged to hold hearings on thousands of claims with respect to which the manufacturer had not produced any evidence meeting the requirement of law." (Br. 29).[28]

Neither the Court of Appeals nor HW&D has stated that a "possibly effective" rating by an NAS-NRC panel constitutes substantial evidence of effectiveness or requires the holding of a hearing. We maintain only that the evidence submitted by HW&D is of such stature as to require a hearing on the question of whether there is substantial evidence of effectiveness of Lutrexin, particularly since FDA has failed to meet its burden of presenting facts to the contrary. FDA knows very well that not many of the 6,000 claims evaluated as "possibly effective" are supported by the kind of evidence submitted by HW&D and that many of the manufacturers making such claims did not bother to request a hearing, even at a time when FDA itself believed that it was obligated to grant the hearing. Yet the Government, in its zeal to denigrate the studies by eminent specialists, submitted by HW&D, has even gone to the extreme of labeling them "anecdotal" (Br. 30).

We show in Part I that the affidavits and medical studies submitted by HW&D cannot rationally be described as an "heterogeneous and unorganized mass of documents." Nor can they, as we have shown, be dismissed as being "testimonial" or "anecdotal" in nature. It is true that HW&D had also submitted a substantial number of letters from practicing physicians requesting the agency to permit them to continue to use Lutrexin in their obstetrical practice. These letters do not detract from the medical studies and affidavits submitted by HW&D. They merely indicate that the doctors took time

[28] The reference here is to *claims* as distinguished from products each of which may have more than one claimed use. See Point III, *supra* at 33.

out from their busy practices to inform FDA that the drug was needed to prevent tragic infant deaths due to premature birth.

With respect to the determination of FDA that Pfizer, Inc. was not entitled to a hearing, Judge Friendly is quoted as saying that ". . . such a determination is peculiarly within the FDA's expertise and we should be reluctant to intrude in medical matters we do not truly understand . . ." (Br. 34). But Judge Friendly also said, in the same sentence ". . . it is apparent even to us laymen that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the regulation" 434 F.2d at 547. The Court below did not think this was true of HW&D's submissions and we believe our analysis of them shows that the court was right.

We have already pointed out that there is no justification for the Government's construction of the Fourth Circuit's opinion to mean that the Commissioner must "negative the almost endless, if remote, possibilities that a hearing might still turn up relevant evidence" (Br. 35). The Court clearly held that HW&D's evidence and the Commissioner's analysis of them created a "genuine question of fact to be resolved at a hearing" (J.A. 180).

HW&D did not, as the Government points out (Br. 38), seek a waiver of the requirements of the regulations. The reasons were that HW&D considered the regulations invalid and that, even under the regulations it was entitled to a hearing (see Points II and III). We would not expect a waiver to be granted if it were requested since FDA has maintained throughout this proceeding that Lutrexin is not effective. It is somewhat disingenuous to imply, even indirectly, that the result might have been otherwise.

IV

RESPONDENT HW&D IS ENTITLED TO A HEARING UNDER REGULATIONS IN EFFECT WHEN THE COMPANY ELECTED TO ACCEPT THE OPPORTUNITY FOR A HEARING PROFFERED IT BY FDA.

An opportunity for a hearing was offered HW&D by the Commissioner on March 22, 1969 (J.A. 12). HW&D made a timely election to avail itself of the opportunity for a hearing (J.A. 14). FDA's regulations in effect at the time provided:

> "If the applicant elects to accept the opportunity for a hearing by written request within 30 days after such notice, a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree" (21 CFR 130.14(b), revised as of January 1, 1969).

It is apparant from the review of FDA's subsequent actions set forth in the Argument, *supra*, under "Background", that FDA failed to follow its own rules when it denied HW&D a hearing and applied retroactively the "summary judgment" regulations.

By failing to follow its own rules FDA deprived HW&D of due process of law and prejudiced the company's rights. *United States* v. *Leahey*, 434 F.2d 7 (1st Cir. 1970); *Hammond* v. *Lenfest*, 398 F.2d 705 (2d Cir. 1968); *Pacific Molasses Co.* v. *FTC*, 356 F.2d 386 (5th Cir. 1966); *Sangamon Valley Television Corp.* v. *United States*, 269 F.2d 221, 224 (D.C. Cir. 1959); *Bucks County Cable TV, Inc.* v. *United States*, 299 F. Supp. 1325 (D. Pa. 1969). The rule was applied in *United States* v. *Heffner*, 420 F.2d 809 (4th Cir. 1969) because of failure

of the Internal Revenue Service to follow its rules relating to warnings by investigators to persons who are suspected of tax fraud, and in *United States ex rel. Brooks* v. *Clifford*, 409 F.2d 700, 706 (4th Cir. 1969), rehearing denied, 412 F.2d 1137 (1969), where the Department of Defense did not follow its procedures for discharge of conscientious objectors from the Army.

In *Elmo Division of Drive-X-Company, Inc.* v. *Dixon*, 348 F.2d 342 (D.C. Cir. 1965), the Federal Trade Commission and appellant's predecessor in interest entered into a consent settlement providing that the settlement could be set aside as provided in Rule V(f) of the Commission's Rules of Practice. Under that rule, if the settlement was reopened and set aside the Commission could *thereafter* undertake corrective action by adversary proceedings as to any acts or practices not prohibited by the settlement. It was alleged that the Commission side-stepped the reopening procedures and issued a new complaint which would result in a second trial upon the same charges. The court held that the Commission was required to abide by its own rule and that "the incorporation of [Rule V(f)] into the consent order 'vested' appellant with the right of a reopening hearing". 348 F.2d at 346.

Here, FDA effectively incorporated in its notice of opportunity for a hearing its rule that a hearing would be held upon acceptance of the proffered opportunity. In any event the rule itself was clearly complied with by petitioner and petitioner was thus "vested" with the right of a hearing.

In *Greene* v. *United States*, 376 U.S. 149 (1964) petitioner claimed compensation for loss of earnings resulting from a discharge from employment with a government contractor, because of a revocation of security clearance, which the courts had held was unlawful and

void. A 1955 regulation of the Department of Defense provided for such compensation. While the claim was being processed a new regulation was adopted, in 1960, placing severe conditions on the granting of compensation, which petitioner could not meet.[29] His claim was processed under the new regulation and denied. The court said—

> "Whatever petitioner's rights are, there can be no doubt that they matured and were asserted under the 1955 directive" (376 U.S. at 160).

> "In summary then, we hold that petitioner was entitled as a matter of right to compensation under the 1955 regulation and that, when the Department of Defense rejected his claim, he was not required to proceed administratively under the 1960 regulations . . ." (376 U.S. at 164-165).

See also *Service* v. *Dulles*, 354 U.S. 363 (1957) and *Vitarelli* v. *Seaton*, 359 U.S. 535 (1959).

It is apparent that for reasons of convenience and expediency, FDA has altered its policy of granting hearings under Section 505 to the prejudice of HW&D whose right to a hearing had matured under prior FDA policy. This is not proper agency action. *Upjohn Company* v. *Pennsylvania Railroad Company*, 381 F.2d 4 (6th Cir. 1967). There the Court said:

> "The Commission's only basis for reversal of its prior decision is that after some three years of elapsed time in a proceeding in another matter with the same fact situation, it has adopted a different policy, and therefore seeks to apply retroactively its new policy" (381 F.2d at 5).

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[29] We have shown that HW&D's submissions to FDA do meet the conditions prescribed by the Agency's regulations.

CONCLUSION

For the foregoing reasons, the judgment of the Court of Appeals should be affirmed.

Respectfully submitted,

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